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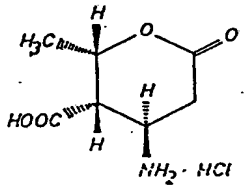
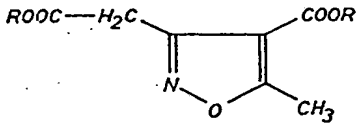
(54) Process for the preparation of an aminolactone

(57) An aminolactone of the formula (I),



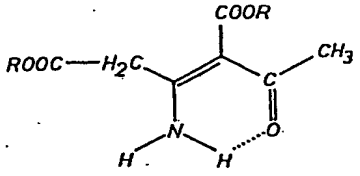
(I)

is produced by a process,
in which
a) a compound of the general formula (III), wherein R represents a C_{1-6} alkyl group,



(III)

is subjected to reduction to yield a compound of the general formula (II),



(II)

wherein R has the same meaning as defined above, and the compound so obtained, in the presence of an alkanecarboxylic acid having a lower alkyl chain in the alkane moiety, is treated with a complex hydride and then with concentrated aqueous hydrochloric acid to yield the compound of the formula (I), or

a_2) a compound of the general formula (II), wherein R has the same meaning as defined above, in the presence of an alkanecarboxylic acid having a lower alkyl chain in the alkane moiety, is treated with a complex hydride and then with concentrated aqueous hydrochloric acid to yield the compound of the formula (I).

The compound (I) is an *intermediate* for the known antibiotic thienamycin and related compounds.

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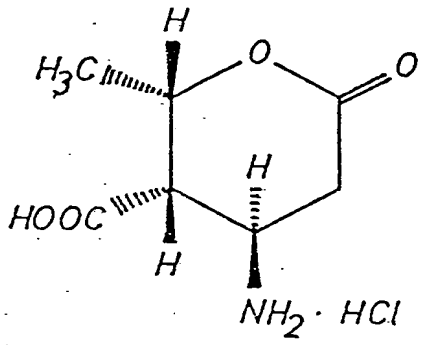
SPECIFICATION

Novel process for the preparation of an aminolactone

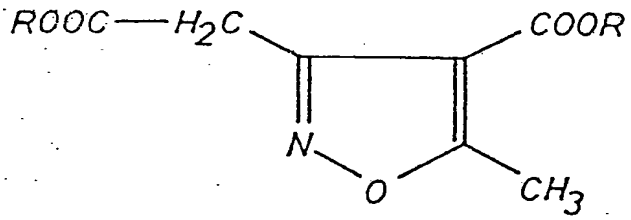
The invention relates to a novel process for the preparation of an aminolactone of the formula (I).



(I)

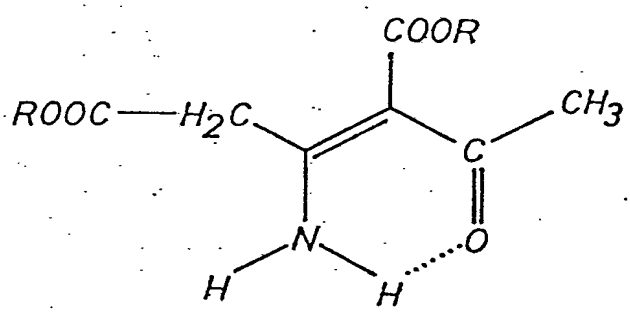
The compound of the formula (I) is an intermediate in the total synthesis of the known antibiotic thienamycin and related compounds. Said total synthesis as well as the process for the preparation of the aminolactone are disclosed in the published European patent specification No. 32400. This process starts from di-ethyl (E)-2-acetyl-3-benzylamino-2-pentenedioate, which first is treated with cyanoborohydride and then with concentrated aqueous hydrochloric acid, and after a reductive debenzylation step the aminolactone is obtained as an oil with a total yield of 20-25%.

Our aim was to find a better synthesis way for the preparation of the aminolactone. It has been found that via the reductive cleavage of an isoxazole derivative of the general formula (III)



(III)

wherein R represents a C_{1-6} alkyl group, a compound of the general formula (II) is obtained,



(II)

wherein R has the same meaning as given above, which is treated with a complex hydride and then with concentrated aqueous hydrochloric acid to yield the crystalline aminolactone with a total yield of 40%. This synthesis route eliminates the introduction and the removal of the protective benzyl group, or in other words, two essential steps of the previous process.

Starting substances of the general formula (III) as well as processes for the preparation thereof were disclosed in our previous Hungarian patent applications Nos. 661/83 (=BE 899007) and 939/84, however, the method of their preparation is exemplified in the present application, too.

Thus, the invention relates to a process for the preparation of an aminolactone of the formula (I), in which

a_1) a compound of the general formula (III), wherein R represents a C_{1-6} alkyl group, is subjected to reduction to yield a compound of the general formula (II), wherein R has the same meaning as given above, and the compound so obtained, in the presence of an alkanecarboxylic acid having a lower alkyl chain in the alkane moiety, is treated with a complex hydride and then with concentrated aqueous hydrochloric acid to yield the compound of the formula (I), or

a_2) a compound of the general formula (II), wherein R has the same meaning as given above, in the presence of an alkanecarboxylic acid having a lower alkyl chain in the alkane moiety, is treated with a complex hydride and then with concentrated aqueous hydrochloric acid to yield the compound of the formula (I).

According to process variant a_1, the synthesis starts from an isoxazole derivative of the general formula (III), wherein R represents a C_{1-6} alkyl group, more particularly an ethyl or an *n*-butyl group. To convert the compound of the general formula (III) into the respective compound of the general formula (II) the starting substance is subjected to reduction, preferably to catalytic hydrogenation. The hydrogenation is accomplished in the presence of a platinum metal catalyst, preferably in the presence of palladium-on-charcoal in a suitable organic solvent, i.e. in a lower alkanol or alkane-carboxylic acid, at atmospheric pressure.

The compound of the general formula (II) is then reacted with a complex hydride, more particularly with sodium borohydride or sodium cyanoborohydride in the presence of a lower alkanecarboxylic acid, examples of which are glacial acetic acid or propionic acid, and then in the same medium is treated with concentrated aqueous hydrochloric acid. The treatment with said acid is accomplished at elevated temperature, preferably at the boiling point of the reaction mixture.

According to a particularly preferred embodiment of the invention, the three reaction steps are carried out without recovering any of the intermediates, thus e.g. in glacial acetic acid in a one pot synthesis directly the aimed compound is obtained, which can be recovered after evaporation and crystallization.

The invention is elucidated in detail by the aid of the following non-limiting Examples.

Example 1

Dibutyl (E)-2-acetyl-3-amino-2-pentenedioate

20 g. (0.067 mole) of *n*-butyl 5-methyl-4-*n*-butoxycarbonylisoxazole-3-yl-acetate is dissolved in 130 ml of methanol and is hydrogenated in the presence of 2 g. of palladium-on-charcoal at atmospheric pressure, at ambient temperature. When the hydrogenation has been completed, the reaction mixture is filtered off, and the filtrate is evaporated. The residue is triturated with pentane to give 17.8 g. (88%) of the crystalline title compound. Mp.: 45-46°C (pentane).

^{1}H-NMR ($CDCl_3$): δ0.93 t (3H); 0.95 t (3H); 1.15-1.9 m (8H); 2.29 s (3H); 3.6 s (2H); 4.15 t (2H); 4.18 t (2H).

Two processes for the preparation of the starting substance are given below as method A and method B.

Method A

A_1) To a solution of 229 g. (10 mmoles) of ethyl *trans*-5-methyl-4-methoxycarbonyl-4,5-dihydroisoxazole-3-yl-acetate in 7.5 ml. of tetrahydrofurane a solution of 5.68 g. (34 mmoles) of potassium iodide and 2.68 g. (10.5 mmoles) of iodine in 25 ml. of water is added and the reaction mixture is refluxed for 6 hours under stirring. The excess of iodine is decomposed with sodium hydrogen sulfite and then the reaction mixture is extracted five times with 10 ml. portions of dichloromethane. The organic layers are combined, washed twice with 10 ml. portions of saturated aqueous sodium chloride solution and finally the organic layer is dried over magnesium sulfate, filtered and the filtrate is concentrated. The residue is triturated with ether to yield 1.56 g. (79%) of crystalline 5- -methyl-4-methoxycarbonylisoxazole-3-yl-acetic acid. Mp.;135°C.

IR (KBr): 3500-2400, 1730 (sh), 1710, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.63 s (3H); 3.76 s (3H); 3.88 s (2H); 10.10 s (1H).

A_2) To 1.99 g. (10 mmoles) of 5-methyl-4-methoxycarbonylisoxazole-3-yl-acetic acid prepared according to step A_1, 10 ml. of water and 10 ml. of concentrated aqueous hydrochloric acid are added, and the emulsion so obtained is refluxed for two hours. The resulting solution is clarified in hot state, filtered off and the filtrate is concentrated to the half of its volume. Upon cooling the residue crystallizes. The crystalline product is filtered off and dried yielding 1.78 g. (96%) of 4-carboxy-5-methylisoxazole-3-yl-acetic acid. Mp.: 230° (Water).

IR (KBr): 3600-2400, 1720, 1690, 1610 cm^{-1}.

^{1}H-NMR (D_2O): δ 2.55 s (3H); 3.85 s (2H).

^{1}H-NMR (DMSO-d_6): δ 2.4 s (3H); 3.55 s (2H).

A_3) 13 g. (70.2 mmoles) of 4-carboxy-5-methyl-isoxazole-3-yl-acetic acid prepared according to step A_2) are refluxed in a mixture of 60 ml. of *n*-butanol, 150 ml. of benzene and 15 ml. concentrated sulphuric acid for 16 hours using a reflux condenser equipped with a water separator. Then the reaction mixture is poured onto ice. The phases are separated. The aqueous layer is extracted twice with 75 ml. portions of benzene. The organic phases are combined, washed twice with 100 ml. portions of water, then twice with 75 ml. portions of 5% aqueous solution of sodium hydrogen carbonate and then twice again with 75 ml. portions of water. The organic layer is dried over calcium chloride and then the solvent is distilled off in vacuo to give 23 g. product as an oil, directly applicable without further purification. If desired, it can be purified by distillation in vacuo (Bp.: 130-131 °C/0.1 Hgmm) to yield the pure *n*-butyl 5-methyl-4-*n*-butoxycarbonylisoxazole-3-yl-acetate.

Method B)

B_1) 350 g. (1.88 moles) of α-ethoxymethylene-acetoacetate are dissolved in 400 ml. of ethanol. To this solution 154 g. (2.2 moles) of hydroxylamine hydro-chlorid in 500 ml. water and 180 g. (2.2 moles) of sodium acetate are added, and the resulting solution is refluxed for 30 minutes. The reaction mixture is poured into 2 liters of water and the phases are separated. The aqueous layer is extracted three times with 250 ml. portions of dichloromethane, the extracts are combined with the organic layer and washed twice with 300 ml. portions of water. The phases are separated, and from the organic layer the dichloromethane is distilled off in vacuo to give 281 g. (96%) of ethyl 5-methyl-4-isoxazolecarboxylate; b.p.: 58-60 °C (0.3 Hgmm), which can be used in the further reaction steps without purification.

^{1}H-NMR ($CDCl_3$): δ 1.4 t (3H); 2.7 s (3H); 4.25 q (2H); 8.5 s (1H).

B_2) 2.81 g. (1.81 moles) of the product obtained in step B_1) are refluxed in a mixture of 200 ml. of glacial acetic acid, 200 ml. of water and 200 ml. of concentrated aqueous hydrochloric acid for 8 hours. Then the reaction mixture is evaporated to dryness. To the residue 400 ml. of acetone are added and is then distilled off. The residue is dried to give 201 g. (87%) of 5-methyl-4-isoxazolecarboxylic acid; m.p.: 146-147°C (toluene).

B_3) To 201 g. (1.58 moles) of the product obtained in step B_2) 350 ml. of thionyl chloride are added stirring within 10 minutes, and then the reaction mixture is refluxed on an oil bath of 120 °C temperature over one hour. The excess of the thionyl chloride is distilled off and the residue is purified by distillation in vacuo to yield 191 g. (83%) of 5-methyl-4-isoxazolecarboxylic acid chloride; bp.: 100-102 °C/18 Hgmm.

Analysis calculated for $C_5H_4ClNO_2$ (145.55):

C 41.25; H 2.77; N 9.68; Cl 24.36%;

found: C 41.17; H 2.92; N 9.57; Cl 24.22%.

B_4) 66.5 g. (2.73 atoms) of magnesium chips are refluxed in a mixture of 20 ml. of ethanol and 1 ml. of carbon tetrachloride. To this boiling mixture 436 ml. (2.73 moles) of diethyl malonate are added in a mixture of 600 ml. benzene and 140 ml. of ethanol within an hour and thereafter the reaction mixture is refluxed for additional 3 hours. About a 500 ml. portion of the solvent is distilled off from the reaction mixture and to the residue first 400 ml. of dioxane and then in 200 ml of benzene 191 g. of the product obtained in step B_3) are added under vigorous stirring at 35-40°C. The reaction mixture is stirred for additional 10 minutes, then cooled and poured into a mixture of 400 ml of concentrated aqueous hydrochloric acid, 600 g. of ice and 1 liter of water. The phases are separated, the aqueous layer is extracted twice with 300 ml. portions of benzene. The organic layers are combined and washed first with a mixture of 80 ml. of concentrated aqueous hydrochloric acid and 400 ml. of water and then twice with 400 ml. portions of water. The organic layer is filtered, and its benzene content is distilled off. To the residue first 1 liter of dichloro-methane is added and distilled off, and then the excess of the diethyl malonate is removed over an oil bath of 135-140 °C temperature (bp.: 70--80 °C/0.4 Hgmm; about 230 ml.). Upon cooling from the residue crystalline ethyl 1-ethyoxycarbonyl-2-hydroxy--2-(5-methyl-4-isoxazolyl)acrylate is obtained with a yield of 330 g. (94%), bp.: 140-144 °C/0.4 Hgmm; mp.: 56 °C (1:1 ether-hexane).

^{1}H-NMR ($CDCl_3$); ;; 1.3 t (3H); 2.7 s (3H); 4.25 q (2H); 4.9 s (1H); 8.5 s (1H).

B_5) 292 g. (1.08 moles) of the product obtained in step B_4) is refluxed in 1 liter of ethanol with 100 g. (1.45 moles) of hydroxylamine hydrochloride. Then the reaction mixture is concentrated, the warm residue is dissolved in 1.2 liters of dichloromethane and filtered. The precipitate is washed twice with 200 ml. portions of dichloromethane. The washings are combined with the filtrate, washed twice with 300 ml. portions of water. The organic layer is concentrated in vacuo. To the residue 750 ml. of dichloromethane is added and then distilled off, the residue is triturated with 120 ml. of ethyl acetate and is left to stand at 0 °C temperature. The crystals are filtered, washed twice with 25 ml. portions of cold ethyl acetate, then twice with 200 ml. portions of *n*-hexane and dried to yield 154 g. (62 %) of ethyl 3-(5-methyl-4-isoxazolyl)-5-hydroxy--4-isoxazolecarboxylate; mp.: 153-154 °C (ethyl acetate). ^{1}H-NMR (DMSO-d_6): δ 1.1 t (3H); 2.4 s (3H); 4.0 q (2H); 8.6 s (1H); 11.0 s (1H).

B_6) 154 g. (0.646 mole) of the product obtained in step B_5) is refluxed in 650 ml. of acetic acid in the presence of 14 ml. of concentrated sulphuric acid for 15 minutes. After the evolution of carbon dioxide has terminated, 40 g. of sodium acetate is added to the solution which is then concentrated in vacuo. To the residue 300 ml. of water is added and is extracted twice with 500 ml. portions of dichloromethane. The organic layers are combined, washed twice with 250 ml. portions of water and the organic layer is concentrated. First 500 ml. of dichloromethane and then 300 ml. of *n*-heptane is distilled off from the residue which finally is recrystallized from 130 ml. of 2-propanol. The crystals are filtered, washed twice with 15 ml. portions of ice--cold 2-propanol and then twice with 75 ml. portions of *n*-hexane and dried in the air to yield 93.4 g (87 %) of 3-(5-methyl-4-isoxazolyl)-4,5-dihydro-5-isoxazolone; mp. 94-95 °C.

^{1}H-NMR ($CDCl_3$): δ 2.7 s (3H); 3.8 s (2H); 8.4 s (1H).

B_7) To a solution of 57 g. (1.42 moles) of sodium hydroxide in 350 ml. of water, 93.4 g. (0.563 mole) of the compound obtained in step B_6) are added in one portion, under stirring at 25°C. Stirring is continued for about 2 minutes while the temperature raises to about 70 °C. The reaction mixture is cooled on an ice-water bath and then 150 ml. of concentrated aqueous hydrochloric acid is added to the mixture which is then repeatedly cooled. The reaction mixture is extracted first with 300 ml. and then twice with 150 ml. portions of dichloromethane. The phases are separated, the organic layer is washed twice with 80 ml. portions of saturated aqueous sodium chloride solution and then is concentrated in vacuo. From the resi-

du first 250 ml. of dichloro-methan and then 150 ml. of *n*-hexane ar distilled off. From the residue upon standing crystalline 4-cyano-5--methyl-3-isoxazoleacetic acid is obtained with a yield f 91.5 g. (98%); m.p.: 90-91 °C (benzene).
^{1}H-NMR ($CDCl_3$): δ 2.6 s (3H); 4.0 s (2H).

B_8) In a mixture of 100 ml. of water and 100 ml. of concentrated aqueous hydrochloric acid 91.5 g. (0.55 mole) of the compound obtained in step B_7) are refluxed for 3 hours. The reaction mixture is cooled, the precipitated product is washed twice with ice-cold water and dried in the air to give 95.7 g. (92%) of 4-carboxy-5-methyl-3-isoxazoleacetic acid, a product with identical characteristics as given in step A_2).

Example 2
(2RS, 3RS, 4SR)-4-amino-2-methyl-6-oxo-tetra-hydropyrane-3-carboxylic acid hydrochloride

10 g. (0.0334 mole) of dibutyl (E)-2-acetyl–3-amino-2-pentenedioate prepared according to Example 1 are dissolved in 60 ml. of glacial acetic acid. To this solution 3.8 g. (100 mmoles) of sodium borohydride are added under stirring and external cooling over about 2 hours. The reaction mixture is left to stand at room temperature overnight, thereupon is concentrated in vacuo. The residue is partitioned between 100 ml. of 10% aqueous sodium carbonate solution and 100 ml of ethyl acetate and then solid sodium carbonate is added until the bu[illegible]bling is ceased. The phases are separated, the aqueous layer is back-extracted twice with 20 ml. portions of ethyl acetate. The organic layers are combined, dried over magnesium sulfate, filtered and the filtrate is concentrated. To the residue 40 ml. of 20% aqueous hydrochloric acid solution are added, the mixture is refluxed over 5 hours, then concentrated. The residue is dissolved in 10 ml. of concentrated aqueous hydrochloric acid at 40-50 °C, then cooled to −10°C to give 3g. (43%) of the title compound as a crystalline solid; mp.: 150-155 °C (dec.)
^{1}H-NMR (CD_3OD): δ 1.36 d (3H, J = 6.5 Hz); 2.82 t (1H, J = 3.5 Hz); 2.85 d (2H, J = 6.5 Hz); 3.98 dt (1H. J = 6.5 and 3.5 Hz); 4.30 dq (J = 6.5 and 3.5 Hz).

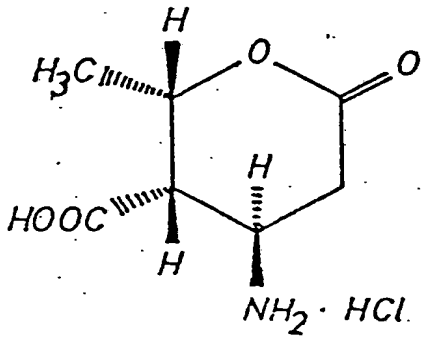
Example 3
(2RS, 3RS, 4SR)-4-amino-2-methyl-6-oxo-tetra-hydropyrane-3-carboxylic acid hydrochloride

70 g. (0.235 mole) of *n*-butyl (5-methyl-4--*n*-butoxycarbonylisoxazole-3-yl)-acetate are dissolved in 350 ml. of glacial acetic acid, and are hydrogenated in the presence of 14 g. of palladium-on-charcoal catalyst at atmospheric pressure. The temperature of the reaction mixture araises to about 40 °C. After the reaction has been finished, the catalyst is filtered off, and to the filtrate 26.8 g. (0.705 mole) of sodium borohydride are added under external ice cooling within about 2 hours. The reaction mixture is stirred at ambient temperature for 3 hours, left to stand overnight and then concentrated in vacuo. The residue is partitioned between 300 ml. of ethyl acetate and 300 ml. saturated aqueous sodium hydrogen carbonate solution, then under vigorous stirring solid sodium hydrogen carbonate is added until the bubbling is ceased. The phases are separated, the aqueous layer is extracted twice with 50 ml. portions of ethyl acetate. The organic layers are combined, dried over magnesium sulfate, filtered and the filtrate is concentrated.

The residue is taken up with 200 ml. of 20% aqueous hydrochloric acid solution, refluxed for 5 hours and then concentrated. The residue is dissolved in 70 ml. of concentrated aqueous hydrochloric acid under moderate heating and then crystallized in a deep freezer to give 19.8 g. (40%) of the title compound. The physical constants are identical with those given in the previous example.

CLAIMS

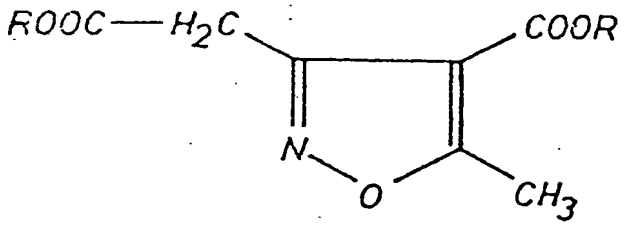
1. A process for the preparation of an aminolactone of the formula (I),



(I)

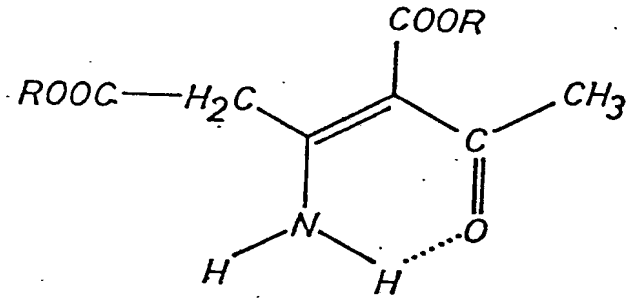
which comprises

a_1) reducing a compound of the general formula (III),



(III)

wherein R represents a C_{1-6} alkyl group, to yield a compound of the general formula (II),



(II)

wherein R has the same meaning as given above, treating the latter compound in the presence of an alkanecarboxylic acid having a lower alkyl chain in the alkane moiety, with a complex hydride and then with concentrated aqueous hydrochloric acid and recovering the amino-lactone, or

a_2) treating a compound of the general formula (II), wherein R has the same meaning as given above, in the presence of an alkanecarboxylic acid having a lower alkyl chain in the alkane moiety, with a complex hydride and then with concentrated aqueous hydrochloric acid, and recovering the aminolactone.

2. A process of claim 1, method a_1) wherein the reduction is catalytic hydrogenation.

3. A process of claim 1, method a_1 or a_2, wherein the complex hydride is sodium borohydride or sodium cyanoborohydride.

4. A process of claim 1, substantially as hereinbefore described with reference to the Examples.

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